UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,586	10/17/2001	George A. Gaitanaris	50001/002005	7567

21559 7590 09/08/2005

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
QIAN, CELINE X	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,586	GAITANARIS, GEORGE A.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-13,18 and 20-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-13,18 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/16/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5-23

DETAILED ACTION

Claims 1, 2, 6-13, 18, 20-24 are pending in the application.

This Office Action is in response to the Amendment filed on 6/16/05.

Response to Amendment

The rejection of claims 1, 2, 6-13, 18, 20-24 under 35 U.S.C. 112 1st paragraph is moot in view of the new ground of rejection under 35 U.S.C. 103 (a) for reasons discussed below.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6-8, 20, 21, 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furth et al (1994, PNAS, Vol.91, pages 9302-9306, IDS), in view of Friedrich et al (1991, Genes and Development, Vol. 5, pages 1513-1523).

Furth et al. teach a transgenic mouse comprising a tetracycline responsive binary system comprising a tetracycline-controlled trans-activator protein (rTA) and the activating domain of viral protein VP16 of herpes simplex virus, which induces transcription from a minimal promoter fused to seven tet operator sequence in the absence of tetracycline, wherein this promoter is operably linked to a luciferase or β-gal reporter gene (see page 9303, 2nd col., 2nd paragraph). Furth et al. further teach that this system is useful for experiments designed to address certain biological questions in transgenic animals, such as temporal control of the induction of growth

modulators, oncoproteins, and other proteins participating in developmental processes and provide further definition to their roles in normal growth and turmorigenesis. Furth et al. also teach that the system can be used to study the effects of expressing potentially deleterious gene, and combined with one of the site-specific recombinase to delete genes at specific time points during development. However, Furth et al. do not teach such a system, wherein the transgene encoding the regulatory protein is integrated into an endogenous gene of said mouse such that the endogenous gene is mutated and said gene is positioned for expression under the control of the promoter of said gene (see page 9306, 1st col., last paragraph).

Friedrich et al. teach a transgenic mouse comprising in its genome a transgene comprising a fusion of β-gal and neomycin phosphotransferase gene under the control of a promoter of an endogenous gene (see page 1514, 1st col., 2nd paragraph and Figure1), wherein the fusion gene is placed downstream of a splice acceptor sequence (see page 1514, 1st col., 3rd paragraph and Figure 1). Friedrich et al. also teach the transgene further comprises retroviral packaging and integration sequences isolated from a moloney murine leukemia virus (see page 1521, 2nd col., 1st paragraph). Friedrich et al. teach that such promoter traps combine the ability to select for insertions within genes with the ability to follow the activity of the tagged gene by β-gal expression, and perform functional analysis of the gene.

It would have been obvious to one of ordinary skill of art to make a transgenic mouse comprising the binary temporal control system as taught by Furth et al. and modifies the transgenic mouse by inserting the regulatory protein into an endogenous gene and utilize the endogenous protein taught by the Friedrich et al. The ordinary skilled artisan would have been motivated to do so not only to study the function of the mutated gene (as taught by Friedrich),

but also provides a gene regulatory system that utilizes the advantage of tissue specific expression of an endogenous gene. The level of skill in the art of molecular cloning is high. Absent evidence to the contrary, one of ordinary skill of the art would have reasonable expectation of success to make a transgenic mouse comprising a transgene comprising a regulatory protein under the control of an endogenous promoter, and a second transgene having a promoter that is regulated by the regulatory protein as claimed. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Furth et al., in view of Friedrich et al., as applied to claims 1, 2, 6-8, 20, 21, 23 and 24 above, and further in view of Zhang et al (1996, BBRC, vol.227, pages 707-711).

The teaching of Furth and Friedrich et al. are discussed above. However, Furth and Friedrich et al. do not teach a marker protein as a fusion protein of a green fluorescent protein and neomycin phosphotransferase.

Zhang et al. teach several reporter genes, such as secreted alkaline phosphatase, B-gal, firefly luciferase, CAT and GFP can be used in *in vivo* reporter assays (see page 707, 3rd paragraph). Zhang et al. further teach that GFP is an important reporter because it has advantages over other reporter for not requiring additional cofactors, substrates, or additional gene products. Zhang et al. further teach the generation of a humanized EGFP that has great sensitivity and stability (see bridging paragraph of 708 and 709).

The obviousness for making a transgenic mouse as comprising a transgene which encodes a regulatory protein under the control of an endogenous gene promoter and a second transgene that is regulated by said regulatory protein is discussed above. It would have been

obvious to one of ordinary skill in the art to replace the β-gal marker protein with GFP based on the teaching of Zhang et al. The ordinary skilled artisan would have been motivated to do so because GFP signal can be observed directed without additional staining or enzymatic reaction. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to make a transgenic mouse as comprising a regulatory protein under the control of an endogenous promoter and further comprise a GFP and neomycin phosphotransferase fusion protein as a marker. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Furth et al. and Friedrich et al., as applied to claims 1, 2, 6-8, 20, 21, 23 and 24 above, and further in view of Bremer et al.

The teaching of Furth and Friedrich et al. are discussed above. However, Furth and Friedrich et al. do not teach the transgene further comprises a recognition sequence recognized by a yeast VDE DNA endonuclease.

Bremer et al. teach a VDE endonuclease from *Saccharomyces crevisiae* and further teach that the VDE cleavage sites can uniquely mark specific genome locations.

The obviousness for making a transgenic mouse as comprising a transgene which encodes a regulatory protein under the control of an endogenous gene promoter and a second transgene that is regulated by said regulatory protein is discussed above. It would have been obvious to an ordinary skilled artisan to insert VDE recognition sites into the transgene because Furth et al. has taught the binary system of can be combined with one of the site-specific

recombinase and use to delete genes at specific time points during development. VDE recombinase system is one of the known recombinase that can be used in such a way to regulate transgene expression in mouse. One of ordinary skill in the art would have been motivated to insert the VDE recognition sites into the transgene to achieve temporal regulation of the transgene expression. The level of skill in the art is high. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation to insert VDE recombinase recognition sites to the transgene. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Furth et al. and Friedrich et al., as applied to claims 1, 2, 6-8, 20, 21, 23 and 24 above, and further in view of Smith et al. (US 6, 150,169)

The teaching of Furth and Friedrich et al. are discussed above. However, Furth and Friedrich et al. do not teach a transgenic mouse as comprising the first transgene which comprises an IRES operably linked to said regulatory gene.

Smith et al. teach DNA constructs that contain expression unit of an IRES coupled to a heterologous gene sequence. Smith et al. teach that when such a construct is introduced into a host genome, the heterologous gene is under the control of regulatory elements of the host gene. Smith et al. teach that translation of the heterologous gene is enabled by the IRES 5' to the open reading frame, which results in greater efficiency of translation.

The obviousness for making a transgenic mouse as comprising a transgene which encodes a regulatory protein under the control of an endogenous gene promoter and a second transgene that is regulated by said regulatory protein is discussed above. It would have been

obvious to an ordinary skilled artisan to insert IRES 5' to the regulatory protein in the first transgene based on the combined teaching of Furth et al., Friedrich et al. and Smith et al. One of ordinary skill in the art would be motivated to do so because Smith et al. teach that inserting an IRES 5' to the heterologous gene would enable greater translation efficiency once the construct is integrated into a host genome. The level of skill in the art is high. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation to insert an IRES site in the first transgene 5' to the sequence encoding the regulatory protein. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Furth et al. and Friedrich et al., as applied to claims 1, 2, 6-8, 20, 21, 23 and 24 above, and further in view of Borrelli et al. (1988, PNAS, Vol. 85, pages 7572-7576).

The teaching of Furth and Friedrich et al. are discussed above. However, Furth and Friedrich et al. do not teach a transgenic mouse as comprising the second transgene encoding a cell ablation factor.

Borrelli et al. teach a toxic vector whose action is based on the targeted expression of the herpes simplex virus 1 thymidine kinase gene product in cultured cells or transgenic animals. Borrelli et al. further teach that this vector is useful to study lineage formation in cultured cells and transgenic animals (see abstract).

The obviousness for making a transgenic mouse as comprising a transgene which encodes a regulatory protein under the control of an endogenous gene promoter and a second transgene that is regulated by said regulatory protein is discussed above. It would have been

obvious to an ordinary skilled artisan to make a transgenic mouse as claimed with the second transgene encoding a toxic gene (cell ablation factor) as taught by Borrelli because Borrelli et al. has taught that said vector is useful to study lineage formation in cultured cells and transgenic animals. One of ordinary skill in the art would have been motivated to use a transgenic mouse depleted with a certain cell lineage to study critical events in lineage formation and organogenesis, wherein such depletion is under temporal regulation of the first transgene expression. The level of skill in the art is high. Absent evidence to the contrary, one of ordinary skill in the art would have reasonable expectation to use the thymidine kinase gene product as the cell ablation factor. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER